Natural History of Hepatitis B Virus Infection in Asian Countries

Jia-Horng Kao, Ph.D., M.D., Ding-Shinn Chen

Hepatitis Research Center, Graduate Institute of Clinical Medicine, and Department of Internal Medicine, National Taiwan University College of Medicine and National Taiwan University Hospital, Taipei, Taiwan

Hepatitis B virus (HBV) infection is a global health problem and causes a wide spectrum of clinical manifestations, ranging from acute or fulminant hepatitis to various forms of chronic liver disease, including inactive carrier state, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Most HBV carriers in the Asian-Pacific region acquire the virus during birth or early childhood. Liver injury associated with HBV infection is predominantly mediated through immune mechanisms. The natural history of Asian HBV carriers who are infected early in life can thus be divided into three phases based on the virus-host interaction. In the immune-tolerance phase, patients are positive for hepatitis B e antigen (HBeAg) and have high serum HBV DNA levels, but have little evidence of liver damage. In the following immune clearance phase, characterized by seroconversion of HBeAg and decreasing serum HBV DNA level, asymptomatic HBV carriers start to have bouts of liver inflammation and hepatitis flare or acute exacerbation. In the low-replicative or integration/residual phase, serum hepatitis B surface antigen (HBsAg) persists in low levels, HBeAg is no longer detectable, patients are usually asymptomatic, and liver disease is in remission. However, a small proportion of patients continue to have moderate levels of HBV replication and active liver disease. These HBeAg-negative chronic hepatitis B patients may have HBV variants that cannot produce HBeAg due to precore or core promoter mutations. In Asians, the frequency and severity of acute hepatitis flare during the immune-clearance phase has been associated with the progression of liver disease. In addition, early seroconversion from HBeAg to the corresponding antibody (anti-HBe) generally indicates a favorable outcome, because it is usually associated with the cessation of virus replication and non-progressive liver disease. On the contrary, late or no HBeAg seroconversion after multiple hepatitis flares may accelerate the progression of chronic hepatitis to cirrhosis, and, therefore, has a poor clinical outcome. Other factors identified as predictors of decreased survival include male gender, older age, presence of cirrhosis, persistence of ALT elevations, co-infection with HCV or HDV, and family history of HCC. Recently, new viral factors predictive of clinical outcomes have been identified. Three large-scale, population-based prospective cohort studies (7 townships in Taiwan, Haimen city in China, and Philadelphia in the US) of Asian HBV carriers aged between 25-65 years all indicated that the best predictor of adverse outcomes (cirrhosis, HCC, and death from liver disease) in chronic HBV infection is the serum HBV DNA level at enrollment, independent of HBeAg status, baseline serum ALT level, and other risk factors. The higher the baseline HBV DNA level, the higher the incidence of adverse outcomes over time. In addition, several hospital-based cohort or case control studies from Taiwan and Hong Kong indicated that

baseline HBV DNA level, HBV genotype C, basal core promoter mutation, and pre-S deletion are associated with increased risk of liver disease progression as well as HCC development. In conclusion, the lessons learned from the natural history of chronic HBV infection in Asian adult HBV carriers can help us better define the clinical threshold as well as therapeutic endpoint of “safe” HBV DNA level (e.g., 10,000 copies or 2,000 IU/mL) for the prevention of long-term liver-related complications in patients during later phases of chronic HBV infection.

References

1. Chen BF, Liu CJ, Jow GM, Chen PJ, Kao JH, Chen DS. Higher prevalence and mapping of pre-S deletion in chronic hepatitis B virus carriers with cirrhosis and hepatocellular carcinoma. *Gastroenterology* 2006;130:1153-68.
2. Chu CJ, Hussain M, Lok AS. Hepatitis B virus genotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus genotype C. *Gastroenterology* 2002;122:1756–62.
3. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006;295:65-73.
4. Chen DS. From hepatitis to hepatoma: lessons from type B viral hepatitis. *Science* 1993;262:369-70.
5. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting liver cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678-86.
6. Kao JH, Chen PJ, Lai MY, Chen DS. Hepatitis B genotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology* 2000;118:554–9.
7. Kao JH, Chen DS. Global control of hepatitis B virus. *Lancet Infect Dis* 2002;2:395-403.
8. Kao JH, Chen PJ, Lai MY, Chen DS. Basal core promoter mutations of hepatitis B virus increase the risk of hepatocellular carcinoma in hepatitis B carriers. *Gastroenterology* 2003;124:327-34.
9. Kao JH, Chen DS. HBV genotypes: epidemiology and implications regarding natural history. *Current Hepatitis Report* 2006;5:5-13.
10. Liu CJ, Chen BF, Chen PJ, Lai MY, Huang WL, Kao JH, Chen DS. Role of hepatitis B viral load and core promoter mutation on hepatocellular carcinoma in hepatitis B carriers. *J Infect Dis* (in press).
11. Lok AS. Prevention of hepatitis B virus-related hepatocellular carcinoma. *Gastroenterology* 2004;127(5 Suppl 1):S303-9.
12. McMahon BJ. Epidemiology and natural history of hepatitis B. *Semin Liver Dis* 2005;25Suppl1:3-8.
13. Ni YH, Chang MH, Wang KJ, et al. Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma. *Gastroenterology* 2004;127:1733-8.
14. Sanchez-Tapias JM, Costa J, Mas A, Bruguera M, Rodes J. Influence of hepatitis B virus genotype on the long-term outcome of chronic hepatitis B in western patients. *Gastroenterology* 2002;123:1848–56.
15. Sherman M. Predicting survival in hepatitis B. *Gut* 2005;54:1521-3.

16. Yuen MF, Yuan HJ, Wong KH, Yuen JC, Wong WM, Chan AO, Wong BC, Lai KC, Lai CL. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005;54:1610-4.
17. Yu MW, Yeh SH, Chen PJ, Liaw YF, Lin CL, Liu CJ, Shih WL, Kao JH, Chen DS, Chen CJ. Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men. *J Natl Cancer Inst* 2005;97:265-272.